REMARKS

Claims 1-4, 7, 8, 12-16, 18, 19, 26-28, 50, and 53-62 are pending. Applicants have added new claims 63-70. Claims 1-4, 7, 8, 12-16, 18, 19, 26-28, 50, and 53-70 will therefore be pending upon entry of the proposed amendments.

New claim 63 depends from claim 1 and requires that the lyophilized didemnin preparation that is present in the kit must be stable for at least 6 months when stored at +4°C in the dark. Support for new claim 63 can be found throughout the specification, e.g., at page 5, lines 3-7.

New claim 64 depends from claim 1 and requires that the weight of the water-soluble material that is present in the lyophilized didemnin preparation must greater than the weight of the didemnin compound that is present in the lyophilized didemnin preparation.

New claim 65 depends from claim 1 and requires that the ratio of the weight of the water-soluble material that is present in the lyophilized didemnin preparation to the weight of the didemnin compound that is present in the lyophilized didemnin preparation must be 25:1.

Support for new claims 64 and 65 can be found throughout the specification, e.g., at the second and third full paragraphs on page 4 and page 5, lines 1 and 2.

New claim 66 depends from claim 12 and requires that the reconstituted pharmaceutical composition must be stable for at least 24 hours after dilution with normal saline up to 1:200. Support for new claim 66 can be found throughout the specification, e.g., at page 5, lines 1 and 2.

New claim 67 depends from claim 12 and requires that the weight of the water-soluble material that is present in the reconstituted pharmaceutical composition must be greater than the weight of the didemnin compound that is present in the reconstituted pharmaceutical composition.

New claim 68 depends from claim 12 and requires that the ratio of the weight of the water-soluble material that is present in the reconstituted pharmaceutical composition to the weight of the didemnin compound that is present in the reconstituted pharmaceutical composition must be 25:1.

Support for new claims 67 and 68 can be found throughout the specification, e.g., at the second and third full paragraphs on page 4 and page 5, lines 1 and 2.

New claim 69 depends from claim 1 and requires that the reconstitution solution of mixed solvents comprises cremophor EL, ethanol, and water for injection in a ratio 15/15/70% (v/v/v).

New claim 70 depends from claim 12 and requires that the reconstituted pharmaceutical comprises: a didemnin compound, a water soluble material, cremophor EL, ethanol, and water for injection, wherein the cremophor EL, ethanol, and water for injection are in a ratio 15/15/70% (v/v/v).

Support for new claims 69 and 70 can be found throughout the specification, e.g., at the third and fourth paragraphs on page 5.

No new matter is introduced by these amendments.

Interview Summary: On April 14, 2009, Applicants' representatives, John T. Kendall and Lee Crews, conducted a telephone interview with Examiner Winston. Applicants' representatives wish to thank the Examiner for his courtesy and helpful comments. During the interview claims 1, 7, 12, and 50 were discussed as was the newly cited Bobee reference.

Claims 1-4, 7, 8, 12-16, 18, 19, 26-28, 50, and 53-62 are rejected as being allegedly unpatentable over Crumb et al., U.S. Patent No. 6,030,943 ("Crumb") in view of Bobee et al., U.S. Patent No. 5,438,072 ("Bobee"). The rejection states, in part (Office Action, pages 4-5):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Crumb et al.'s pharmaceutical composition and/or kit to include the solubilization active ingredient mixture of an alkanol (i.e. ethanol), surfactant and water as taught by Bobee within Crumb's pharmaceutical composition and/or kit because the combined teachings as a whole would create the claimed pharmaceutical composition and/or kit for enhanced injectable delivery of the pharmaceutical composition's active ingredient such as the claimed didemnin compound to a subject. Furthermore, the adjustment of other conventional working conditions (e.g., the substitution of one functional equivalent alkanol for another, determining suitable amount/ranges of each active ingredient within the claimed composition to create solubilization of the pharmaceutical composition, the substitution of one surfactant for the other and placing the reconstitution solution within a container such as a vial), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

This is respectfully traversed.

[I] The Claimed Kits and Reconstituted Pharmaceutical Compositions

[A] The Independent Claims

Claim 1 reads as follows:

A kit comprising firstly a lyophilized didemnin preparation and secondly, and separately contained, a reconstitution solution of mixed solvents,

wherein the lyophilized didemnin preparation comprises a didemnin compound and a water-soluble material;

wherein the reconstitution solution of mixed solvents comprises water for injection, an alkanol, and a nonionic surfactant, wherein the water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and the alkanol is present in an

amount sufficient to allow solubilization of the didemnin compound in the lyophilized didemnin preparation; and

wherein reconstitution of the lyophilized didemnin preparation with the reconstitution solution of mixed solvents provides a parenterally suitable preparation.

Claim 12 reads as follows:

A reconstituted pharmaceutical composition comprising:

a didemnin compound;

a water soluble material;

a nonionic surfactant;

an alkanol; and

water for injection;

wherein the water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and the alkanol is present in an amount sufficient to allow solubilization of the didemnin compound.

[B] As will be discussed in more detail below, the claimed kits and pharmaceutical compositions address some of the problems associated with prior efforts to obtain stable, soluble pharmaceutical preparations that are suitable for the parenteral (e.g., intravenous) administration of a didemnin compound.

[1] ***Didemnin compounds are cytotoxic agents that generally have very low solubility in water***

Didemnin compounds are class of cyclic depsipeptides that exhibit a wide variety of biological activities including antitumor activity (see, e.g., the "Background" section of the specification and the reference cited therein and the paragraph bridging pages 2 and 3 of the specification).

An example of a didemnin compound is "aplidine" (also known and referred to in the art as "dehydrodidemnin B"), which is a potent cytotoxic agent. Aplidine is typically administered by intravenous injection and preferably by infusion over several or more hours. When administered in this fashion, the aplidine needs to be dissolved in water or, alternatively, in a water-miscible solvent(s) that can be diluted in aqueous vehicles normally used for large volume infusion, e.g., saline.

Didemnin compounds, however, generally tend to have very low solubility in water. For example, the solubility of aplidine in water is less than 0.1 mg/mL (see Nuijen, et al., *PDA journal of Pharmaceutical Science and Technology* **2000**, *54*, 193). The solubility of aplidine is higher in some water-miscible solvents, e.g., alkanols. However, the use of such solvents typically does not provide didemnin pharmaceutical preparations having long term stability. The lack of long term stability can be problematic, particularly bearing in mind that generally didemnin compounds (e.g. aplidine) are administered by intravenous infusion, preferably by infusion over periods of up to 24 hours.

[2] ***The claimed kits and pharmaceutical compositions also require that a water soluble material must be present in addition to the didemnin compound***

[a] In order to increase the solubility of the didemnin compound in water while allowing to obtain a stable pharmaceutical preparation, the inventors of the present invention have developed a formulation providing a stable lyophilized didemnin preparation and a solution of mixed solvents for its reconstitution. Developing a lyophilized didemnin formulation was not an obvious solution due to the fact that didemnin should be first dissolved in water prior to the lyophilisation step (i.e. sublimation of water) and then further dissolved in water or, alternatively, in a water-miscible solvent(s). To achieve a stable lyophilized didemnin preparation (e.g., a lyophilized didemnin preparation that is stable for at least 6 months when stored at +4°C in the dark; *cf:* new dependent claim 63), a bulking agent must be included as part of the preparation. See, e.g., the specification at the paragraph bridging pages 1 and 2:

> In practice, there are some difficulties in preparing pharmaceutical compositions of didemnin compounds suited for administration to patients, and there is especially a need for a stable parental pharmaceutical dosage form. More specifically, didemnin compounds such as dehydrodidemnin B, also known as aplidine, require mixing with bulking agents, such as mannitol, for optimal, stable preparation of pharmaceutical dosage forms, in particular lyophilized preparations,

While not wishing to be bound by theory, the bulking agent is believed to increase the dispersibility of the didemnin compound (e.g., aplidine) in the lyophilized preparations of the claims. As a result of this, it is less likely that the didemnin compound will aggregate and form particles during lyophilization. These effects are believed to confer additional stability to the didemnin compound as well as enhanced solubility properties. In addition, the presence of the bulking agent is also thought to facilitate the accuracy of dosing, a useful feature given that didemnin compounds are generally very potent and typically administered in low doses.

[b] Typically, the weight of the bulking agent that is present in the lyophilized didemnin preparation is greater than the weight of the didemnin compound (see new dependent claim 64; see also new dependent claim 67). For example, the ratio of the weight of the bulking agent to the weight of the didemnin compound can be as much as 25:1 (see new dependent claim 65; see also new dependent claim 68).

[c] Since (i) the bulking agent can be (and typically is) the major component of the lyophilized didemnin preparation (see paragraph **[b]** above); and (ii) reconstitution of the lyophilized didemnin preparation with the reconstitution solution of mixed solvents must provide a parenterally suitable preparation (i.e., one that is dilutable in an aqueous vehicle suitable for intravenous administration, such as saline), then a water soluble bulking agent must be used in the lyophilized didemnin preparation (*cf.* dependent claims 8, 13, and 53). A preferred bulking agent for this purpose is the water soluble bulking agent mannitol (*cf.* dependent claims 14 and 54).

Water-soluble bulking agents, such as mannitol, are freely soluble in water, but are not soluble or are only very slightly soluble with other solvents, such as alkanols (i.e., solvents in which a didemnin compound, such as aplidine, can be dissolved). By way of example, Applicants submit for the Office's consideration the specifications of mannitol from the Handbook of Pharmaceutical Excipients. A table showing mannitol's low solubility in alkanols (e.g. ethanol or propan-2-ol) can be found in page 295, last paragraph of column 1.

[3] ***Even though didemnin compounds have very low solubility in water, the reconstitution solution of the claims not only contains water, but can contain water as the major component***

A reconstitution solution containing water, preferably as the major component (e.g., 50-80% -- see dependent claims 7 and 50; e.g., 70% -- see dependent claims 69 and 70), was needed in order to solubilise the water-soluble bulking agent and to avoid the stability problems that can be encountered when the reconstituted pharmaceutical composition is further diluted in a water-based vehicle for intravenous administration. Thus, in the present case, the problem to be solved was to find a reconstitution solution containing water, preferably as the major component, which would also solubilize the didemnin compound and provide a reconstituted pharmaceutical composition having long-term stability.

Surprisingly, it was found that a reconstitution solution containing 70% water, see, e.g., the specification at page 5, lines 13-14, in which the reconstitution solution is "15/15/70 v/v/v Cremophor EL/ethanol/water" (see also dependent claims 69 and 70), could be used. Once reconstituted, the reconstituted preparation could subsequently be dissolved in a perfusion solution. Moreover, it was found that "dilutions of reconstituted product with normal saline up to 1: 200 showed it to be stable at least for 24 after preparation" (see specification at page 5, paragraph 1, this advantage is embodied in new dependent claim 66).

[4] In summary, the inventors have discovered lyophilized didemnin preparations having long term stability. This practical advantage, which *inter alia* significantly extends shelf life of the preparations, is embodied in new dependent claim 63. The presence of a bulking agent is believed to confer the aforementioned stability to the lyophilized preparations. As discussed above, the bulking agent is typically present to a greater extent by weight than the didemnin compound in the preparations (in some cases in a ratio of 25:1).

Didemnin compounds (e.g., aplidine) are typically administered by intravenous injection and preferably by infusion over several or more hours. When administered in this fashion, the didemnin compound needs to be dissolved in water or, alternatively, in a water-miscible solvent(s) that can be diluted in aqueous vehicles normally used for large volume infusion, e.g., saline. As above mentioned, a bulking agent must be included to achieve a stable lyophilized didemnin preparation and typically, the bulking agent is the major component of the lyophilized preparation. As such, a water soluble bulking agent must be used in the lyophilized didemnin preparations of the claims.

So, to achieve stable lyophilized didemnin preparations that are also suitable for intravenous injection (the preferred mod e of administering didemnin compounds), one needs to combine (and ultimately solubilize) two substances that are quite dissimilar with respect to their solubility in water (i.e., the didemnin compound and a water soluble material, e.g., a water soluble bulking agent, e.g., mannitol). This difference in water solubility makes the solubilization of a didemnin (e.g., aplidine) and a water soluble material (e.g., mannitol) in water based vehicles difficult. The inventors, in addressing the aforementioned problem, have discovered that a reconstitution solution that includes water for injection, an alkanol, and a nonionic surfactant is capable of solubilizing both of these dissimilar substances. Once reconstituted, the reconstituted preparation could subsequently be dissolved in a perfusion solution. Moreover, it was found "dilutions of reconstituted product with normal saline up to 1: 200 showed it to be stable at least for 24 after preparation" (see specification at page 5, paragraph 1). This practical advantage, which permits *inter alia* infusion of a didemnin compound over several or more hours, is embodied in new dependent claim 66.

[II] Crumb

[A] Crumb discloses that aplidine can be used as an L-type calcium channel enhancer (Crumb, col. 2, lines 33-34). Crumb teaches that aplidine can be administered "intravenously or by injection" using "liquids" that contain a **single** solvent, namely **water** (see Crumb at col. 6, lines 12-18). A co-solvent (e.g., an alkanol) is never mentioned in Crumb. Further, there is no mention of lyophilized preparations having long term stability. Finally, the sole lyophilised pharmaceutical composition disclosed in Crumb is for intramuscular injection, not intravenous administration.

[B] Applicants wish to conclude their discussion of Crumb by addressing two statements in the Office Action about Crumb.

[1] First, Applicants wish to address page 3, first full paragraph of the Office Action:

> Crumb teach a pharmaceutical composition that may be in a form of a container (i.e. kit is a container and the container described in Crumb is a sterile ampoule) comprising firstly a lyophilized didemnin preparation comprised of a didemnin (i.e. aplidine and dehydrodidemnin) and a water soluble material (i.e. mannitol) and water; secondly a reconstitution solution comprised of a carrier such as water used for the purpose of aiding in the injectable administration of the pharmaceutical to a subject (see, e.g. column 5, lines 66-67 and column 6, lines 12-20).

Applicants respectfully disagree with this characterization of Crumb.

Applicants have reproduced below the following passages from Crumb: **(1)** the paragraph bridging cols. 5 and 6; and **(2)** col. 6, lines 12-20. In passage **(1)**, Applicants have underlined the text corresponding to "column 5, lines 66-67," which is specifically referred to in the above-quoted passage from the Office Action. Passage **(2)** is also underlined in full.

> Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose,

polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, Aplidine can be admixed with carriers and diluents molded into tablets or enclosed in gelatin capsules. The mixtures can alternatively be dissolved in liquids such as ten percent aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection. Such solutions can, if desired, be lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of sterile water for ready intramuscular injection.

Passage **(1)** discloses a list of Crumb's contemplated "carriers, excipients, and diluents" that happens to include "mannitol." No specific pharmaceutical formulation of aplidine is disclosed in Crumb. Passage **(2)** discloses, in somewhat general terms, Crumb's contemplated modes of administration. It is therefore submitted that the above quoted passages from Crumb do not constitute a disclosure of a "a pharmaceutical composition that may be in a form of a container (i.e. kit is a container and the container described in Crumb is a sterile ampoule) comprising firstly a lyophilized didemnin preparation comprised of a didemnin (i.e. aplidine and dehydrodidemnin) and a water soluble material (i.e. mannitol) and water" (Office Action, page 3), as asserted by the Office. Rather, the Office's assertion regarding Crumb appears at most to be the result of picking, choosing, and combining various isolated disclosures in Crumb. Moreover, without the knowledge of the claimed kits and reconstituted pharmaceutical compositions, there is nothing in Crumb that would have even led one to the specific disclosures that were picked and combined by the Office.

[2] Applicants also wish to address the following statement on page 7 of the Office Action (emphasis added):

> Crumb does teaches [*sic.* teach] that one of ordinary skill in the art would **want** to utilize surfactant and/or wetting agents within its pharmaceutical formulation and/or container (**see, e.g., column 6 lines 5-11**).

"Column 6 lines 5-11" of Crumb, which is cited by the Office in the passage above, is reproduced below:

> The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

There is nothing in this passage (or anywhere else in Crumb) that would have led one to "want to utilize surfactant and/or wetting agents" (Office Action, page 7). The term "surfactants" does not even appear in this passage. Rather, the above-quoted passage from Crumb merely provides a listing of optional components that could be included in a formulation. Again, to the extent that Crumb discusses vehicles for injection of aplidine, Crumb teaches only the use of single solvent (water) based vehicles for injection, particularly for injection of aplidine in lyophilized form (Crumb at col. 6, lines 14-20, emphasis added):

> The mixtures can alternatively be dissolved in liquids such as ten percent aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection. Such solutions can, if desired, be **lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of sterile water for ready intramuscular injection**.

In short, there is nothing in Crumb that would have led one to necessarily "want" to modify Crumb's aplidine/water-based, injectable solutions. Furthermore, it is submitted that Crumb is clearly not concerned with aplidine's solubility and let alone with reconstituting a lyophilised composition having components that are quite dissimilar with respect to their solubility in water. A reconstitution solution is not even mentioned in Crumb, let alone a suggestion to use a mixed solvent reconstitution solution comprising a non-ionic surfactant, an alkanol and water for injection.

[III] Bobee

[A] Bobee concerns taxoid-based compositions. Taxoids are quite a bit different from the didemnin compounds of the claims. As will be discussed in more detail below, Bobee discloses additives that can be used to increase dissolution of a taxoid (in the form of a surface-active agent "stock" solution) in a water-based perfusion solution, without forming a gel.

[B] More specifically, Bobee discloses taxoid-based injectable compositions useful for the preparation of a perfusion solution, in which the formation of a gelled phase during the mixing of the compositions with an aqueous solution is avoided or can be broken. Said injectable compositions include:

i) a solution of the taxane derivative in a surface-active agent (stock solution) and

ii) an aqueous solution containing a dilution additive selected from organic compounds having a hydroxyl group or an amine functional group and a molecular weight of less than 200 or sodium chloride.

According to Bobee, these two solutions are preferably mixed immediately before use at the time of injecting into the perfusion bag (which contains the perfusion solution); see column 3, lines 45-50.

Bobee has nothing to do with reconstituting a lyophilized preparation, much less one that includes two substances that are quite dissimilar with respect to their solubility in water. Rather, Bobee is focused on trying to dissolve a taxoid, which again is different from a didemnin compound, into a perfusion solution and doing so *via* an intermediary stock solution and without the formation of a gelled phase during dissolution.

[C] According to Bobee (column 3, lines 14-18), ethanol is one of the compounds that can be used as an additive to increase dissolution of the taxoid in the surface-active agent solution (stock solution) in the perfusion solution. Others include glucose, glycerol, propylene glycol, glycine, sorbitol, mannitol, benzyl alcohol, polyethylene glycols and inorganic salts such

as sodium chloride (Bobee at column 3, lines 19-39). These additives are chosen from the range of additives which are capable of breaking or avoiding the formation of a gelled phase which is formed between the emulsifier (i.e. surface-active agent) containing the derivative of the class of taxoids and the water.

Thus, Bobee relates to different pharmaceutical compositions (i.e. injectable solutions instead of lyophilized preparations) and solves a different problem (increase dissolution of the stock solution containing a taxoid derivative and a surfactant into the perfusion solution instead of reconstituting a lyophilised composition with components soluble in incompatible solvents). Moreover, it refers to taxoid compounds, which have chemical structures that are substantially different from a didemnin (a cyclic depsipeptide).

[IV] The Supreme Court discussed the requirements for making rejections under 35 U.S.C. 103 in *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007, bolded, underline emphasis added).

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.
>
> When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, **a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**. Although common sense

directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, **it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**. This is so because **inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known**.

Thus, a claim is not proved obvious merely by showing that the elements of that claim can be found in the prior art. Rather, the Office must articulate some reason as to why a person of ordinary skill in the art, at the time of the invention, would have combined the elements in the manner required by the claim.

[V] Assuming one had reason to modify Crumb (and Applicants do not concede that this is the case), one would need to make several modifications of, and selections within, the references of record in order to arrive at the claimed kits and reconstituted pharmaceutical compositions. One would at least need to lyophilize Crumb's aplidine with a water soluble material (e.g., a water soluble bulking agent, *cf*: dependent claims 8, 13, and 53; e.g., mannitol, *cf*: dependent claims 14 and 54). There is nothing in either Crumb or Bobee that would have led one to do so, much less expect this modification to result in lyophilized didemnin preparations having long term stability (e.g., a lyophilized didemnin preparation that is stable for at least 6 months when stored at +4°C in the dark; *cf:* new dependent claim 63).

Even if one would have been led to lyophilize Crumb's aplidine with a water soluble material (and Applicants do not concede that this is the case), the skilled person seeking to solubilize such a lyophilized preparation would not have turned to Bobee for guidance. This is discussed in more detail below.

Bobee has nothing to do with reconstituting a lyophilized preparation, much less a preparation that includes two substances that are quite dissimilar with respect to their solubility in water. Rather, Bobee is focused on trying to dissolve an entirely different active ingredient

(i.e., a taxoid), and not a lyophilized mixture of dissimilar components, into a perfusion solution and doing so *via* an intermediary stock solution and without the formation of a gel during dissolution.

If anything, the skilled person seeking to solubilize a lyophilized preparation containing Crumb's aplidine (or any other didemnin compound for that matter) and a water soluble material would have been led away from Bobee. As discussed above, water-soluble bulking agents, such as mannitol, are freely soluble in water, but are not soluble or are only very slightly soluble with other solvents, such as alkanols (i.e., solvents in which a didemnin compound, such as aplidine, can be dissolved). By way of example, Applicants again refer to the Handbook of Pharmaceutical Excipients, which shows that mannitol has a low solubility in alkanols (e.g. ethanol or propan-2-ol). Thus, the skilled artisan seeking to solubilize a lyophilized preparation containing Crumb's aplidine (or any other didemnin compound for that matter) and a water soluble material (e.g., a water soluble bulking agent; e.g., mannitol) would not have selected Bobee's alkanols (e.g., ethanol; *cf*: dependent claims 19, 56-60, and 62) to be part of the reconstitution solution. This is because the skilled artisan would not have selected a solvent that is incompatible with what is typically the major component of the lyophilized preparation (cf: dependent claims 64, 65, 67, and 68).

In conclusion, all the Office appears to have done is show that some elements of the claims can be found in the references of record (this is evident from some of the Office's characterizations of Crumb). However, no reasoned explanation is provided as to why the skilled artisan would have combined these elements in the manner presently claimed. The Office provides no reasoned explanation as to why one would have made even one of the modifications/selections discussed above, much less all of them in combination, and it is submitted that without the knowledge of the claimed kits and reconstituted pharmaceutical compositions, there is nothing in Crumb and/or Bobee that would have even led one to the specific disclosures that were picked and combined by the Office. Further, there is nothing in Crumb and/or Bobee that would have led one to reasonably expect that combining the specific

disclosures in the manner claimed would have resulted in kits and reconstituted pharmaceutical compositions having, e.g., the stability properties claimed in claims 63 and 66, respectively.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUDING FORMALITIES

Applicants submit that all claims are in condition for allowance.

The required fee of $1,110.00 for the Three Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account Authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14620-012US1.

Respectfully submitted,

Date: July 9, 2009

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